Ministry of Health of Ukraine Poltava State Medical University Department of internal medicine No 3 with phthisiology

Approved at the meeting of the Department of Internal Medicine No. 3 with Phthisiology Protocol № _____ "__" 20____ p. Associate Professor, PhD _____ O. Borzykh

Methodical instructions for the independent work of students during the preparation for a practical lesson and in class

Academic discipline	Phthisiology	
Modul №	1	
Theme of the lesson 6	Treatment of patients with tuberculosis: antimycobacterial drugs, protocols of treatment of patients with tuberculosis, pathogenetic and surgical treatment. Curation of patients.	
Course	4	
Faculty	International	
Specialty	Medicine	

Consist by professor A.G.Yareshko Assistent M.V.Kulish

1. **Topicality of the theme:** actuality of theme is determined that today in the whole world the main mean of treatment TB is acknowledge the group of basic ant tuberculosis preparations (ATP), in which included isoniasidum, rifampicinum, pirazinamidum, streptomycin, ethambutol. Due to these preparations modern medicine arrives at curing of patient on TB, diminishes lethal consequences from TB, development of medicinal resistant of MBT warns, provides diminishing of distribution of exciter in an environment and decline of infecting of people TB.

In connection from by growth of primary and second firmness of MBT to PTP and with the purpose of optimization of treatment of sick TB. Last years in a phthisiology all more frequent began to utilize ATP I-th a row, antibiotics of ftorchinolon row. WHO is developed and made to order for treatment in the entire countries of the world the charts of treatment of sick TB are standardized in accordance with categories which are utilized on Ukraine on a draught almost 5 years. Therefore all of future doctors must own this knowledge.

2. Specific objectives:

To analyze: efficiency of the different modes of chemotherapy

To explain: mechanisms of action of PTP

To offer: the ways of increase of efficiency of treatment TB are possible

To classify: ant tuberculosis preparations

To interpret: testimony and contra-indication of application of ATP

To draw: combinations of ATP according to the categories of sick TB

To analyze: by-reactions are possible on ATP

To make: protocol of treatment of sick TB

3. Base knowledge, abilities, skills, are necessary for study themes (interdisciplinary integration)

Names of previous disciplines	Skills are got	
Pharmacology	Pharmacokinetic of ATP. Testimony, contra-indication.	
	Side-reactions.	
Surgery	Surgical methods of treatment TB	
Physiotherapy	Physical therapy methods of treatment TB	

4. Task for independent work during preparation to employment

4.1. List of basic terms, parameters, descriptions which a student must master at preparation to employment:

Term	Determination
Complexity	it is combination of specific and heterospecific treatment, and also
	application of surgical methods
Combination	it is application a few (no less than 3-4) ATP at treatment of sick
	TB according to categories.
Stage	It is a lead through of treatment on the stages: permanent
	establishment is a sanatorium – policlinic.
Indirect action	any undesirable reaction, predefined pharmacological properties of
	medication, which is observed exceptionally at his use in doses,
	made to order for treatment

4.2. Theoretical questions are to employment:

- 1. Specify basic principles of treatment TB.
- 2. What are the phases of treatment patients on TB?
- 3. Classification of ant tuberculosis preparations?
- 4. Name the standard mode of treatment patients on TB 1-th category?
- 5. Name the standard mode of treatment patients on TB II categories?
- 6. Name the standard mode of treatment patients on TB III categories?
- 7. Name the standard mode of treatment patients on TB IV categories?
- 8. What nosotropic methods of treatment are utilized in a phthisiology?
- 9. What surgical methods of treatment are utilized in a phthisiology?
- 10. What by-reactions on ATP, methods of their warning and removal?
- 11. Testimony and contra-indication of ATP.

4.3. Practical works (task) which execute on employment: Initial level

1. What from the resulted preparations does have intracellular activity only?

- A.Streptomycin
- B.Kanamycinum
- C.Pirazinamidum
- D.Ethambutolum
- E.PASK

2. What preparations don't behave to the group 1?

A.Isoniazidum B.Streptomycin C.Rifampicinum D.Ethambutolum E.Etionamid

3. What from the resulted preparations is irreplaceable at treatment TB?

- A.Kanamycinum
- **B**.Ethambutolum
- C.Isoniazidum
- D.Tibon
- E.Ftivazid
- 4. In sick fibrous-cavern TB of lungs, Mbt+. What group of clinical (category) account must a patient be in?
 - A.1 B.II C.III D.IV
- 5. At patient T., 40 years was diagnosed the relapse of pulmonary TB. What group of clinical account the sick is in?
 - A.1 B.2 C.3
 - D.4
- 6. At patient T. dissemination TB is first diagnosed, both the lungs, phase of destruction, Mbt+. What maximal term can a hospital sheet be given out on him?

A.On 1 month B.On 3 months C.On 10 months D.On 2 weeks

7 A woman entered maternity hospital. For it a girl borned 3 kg 800 grammas. The man of woman is ill the opened form of TB.

What tactic of doctor of phthisiologist in this case?

A. To hospitalize a patient in TB permanent establishment, at home to do final disinfection

B.To treat the patient of house, on conditions of observance of ant epidemic regimes

C. To appoint treatment a child

D. To appoint treatment of mother

7. Patient to T. 25 years of diagnosed – FTB of dissemination TB of lungs, destr.+,

Mbt+. Pregnancy is 9 months A. patient is translated to the maternity hospital. A boy borned 4 kg. What tactic of doctor of neonatologist?

A.To do a child the vaccination of BCG

B.To do a child the vaccination of BCG – M

C.To do a child a vaccination in 6 months in policlinic terms

D.Not to do BCG vaccination

- 9. The initial chemotherapy of first found out destructive TB of lungs needs treatment preparations:
 - A.4 HRSZ B.2 HROfE C.2 N2R2S2 D.3HREt
- **10.** At patient a sonitus appeared at treatment of infiltration TB of lungs, lowering of ear. **What preparation is it necessary to abolish?**

A.Isoniazidum B.Rifalexum C.Streptomycin D.Ethambutolum

Theme contents:

1. GENERAL PRINCIPLES OF TREATMENT PATIENTS ON TB

The basic method of treatment TB is polichimiotherapy is the combined therapy with the use of 4-5 chemopreparetion (isoniasidum, pirazinamidum, ethambutolum) and antibiotics of wide spectrum of action for the expressed ant tuberculosis activity (rifampicinum, streptomycin, kanamycinum, ofloxacinum).

The primary objective of treatment TB is proof achievement of stopping of secreting MBT, cicatrisation in the staggered organs and liquidation of clinical signs of disease TB of changes. For this purpose it is necessary steadily to adhere to **basic principles treatments** to which belong: complexity, combination, duration and continuity, timeliness of exposure, individual going near patients, stage and testability of treatment, and his free of chargeness.

I. Complexity treatment is combination of all of accessible methods of treatment (ATP, nosotropic facilities, surgical methods, physical therapy, and sanatorium-resort treatment):

- 1. A basic method of treatment is an etiotropic chemotherapy.
- 2. Nosotropic therapy.
- 3. Surgical treatment.
- 4. Physical therapy treatment.
- 5. Sanatorium-resort treatment.

II. The combined therapy is application a few (no less than 3-4) ATP at treatment of sick TB according to categories. It is related to that the combined therapy prevents development of firmness of MBT, slows the leading out of separate ATP from an organism and thus during great while their higher concentration is saved in blood and fabrics, that an action increases.

III. Protracted and continuous treatment. Optimum duration of treatment in accordance with standards makes 6 - 9 months for patients 1 - III categories. For patients IV after the individual modes precedes a category to 12-18-24 months, even during all of life. The continuous (regular) reception of preparations is diminished by possibility of development of firmness of exciter, and also instrumental in efficiency to treatment. Intermittent a method (over day, 2-3 times per a week) which is inculcated in 1964-1966 is considered continuous.

IV. A timeliness of treatment (early exposure) is treatment in the earliest terms of illness, when it did not purchase heavy motion and there is not disintegration and secreting MBT. What before found out sick on TB and treatment is begun, the more so guarantees on complete convalescence of patient, with less economic expenses. An early exposure is warned by distribution of TB.

V. Individualization of treatment taking into account bearableness of ATP, sensitiveness of MBT to ATP, allergic reactions, bodily and social condition of patient.

VI. Phases of treatment. The first intensive phase is directed on oppression, reproduction of population of MBT, its substantial diminishing and partial sterilization of hearth of specific defeat. The initial (intensive) phase of ATP is completed in the case of stopping of secreting MBT and achievement of positive clinic-x-ray dynamics TB. In the second phase (supporting) conduct daily or intermittent ATP therapy with the purpose of the clinical curing of patient or preparation to surgical interference.

VII. Stage of treatment consists in the lead through of him on the stages: permanent establishment (intensive and phase of under treatment) is a sanatorium (phase of continuous treatment) – ambulatory treatment.

VIII. Testability of treatment – DOTS foresees the reception of ATP a patient in a presence and under control a medical worker.

IX. Continuous. An interruption in treatment more 1-th month results in development of резистентности of MBT and complicates subsequent treatment.

X. Treatment patients on TB necessarily must be *free of charge*, accessible and safe.

Ant tuberculosis preparations are a basic mean of treatment of all of clinical forms TB regardless of his localization.

Classification of anti-TB drugs:

Group 1 - TB drugs and series:

• isoniazid (H);

• rifampicin (R);

- pyrazinamide (Z);
- ethambutol (E).

Group 2 - TB injectable drugs:

- streptomycin (S);
- kanamycin (Km);
- amikacin (Am);
- capreomycin (Cm).

Group 3 - fluoroquinolones:

- ofloxacin (Ofx);
- levofloxacin (Lfx);
- moxifloxacin (Mfx);
- Gatifloxacin (Gfx).

Group 4 - bacteriostatic anti-TB drugs II series:

- Ethionamidum (Et);
- protionamid (Pt);
- cycloserine (Cs);
- terizidone (Trz);
- para-aminosalicylic acid (PAS);
- sodium para-aminosalicylic acid.

Group 5 - drugs of uncertain efficacy (not recommended for routine use of MRI in patients with TB, if necessary, used for patients RRTB if there are no other opportunities to create circuits with 4 anti-TB drugs with 1-4 groups):

- clofazimine (Cfz);
- amoxicillin / clavulanic acid (Amx / Clv);
- clarithromycin (Clr);
- linezolid (Lzd);
- isoniazid in high doses

Description of ant tuberculosis preparations 1 row.

Isoniazidum *Isoniazidi* (*H*) – most effective PTP, is derivative hidrasid of isonicotinic acid (GINK). To this group such preparations belong also, as phtivasid, metasid. Form of issue isoniasid are pills for 0,1; 0,2; 0,3 and 10% solution for 5,0 ml., syrup. Per mouth enter, in muscular, in vein, stream and inhalations, inundations. Appoint during all of course of treatment, which can make from 6 - 9 to 12-18-24 months. Isoniazidum is blocked by the synthesis of albumens in MBT and synthesis of endogenous catalase and the same halts their reproduction. Operates on MBT, which are located endo and out cellular. Indirect action: neuro- and hepatotoxic effect. Toxic reactions are warned setting of vitamins of group B, especially B6, which is a toxicide isoniasid.

Rifampicinum (*Rifampicini*), (*R*) – is also one of the most effective ant tuberculosis preparations. Rifampicinum is a semysintetic antibiotic of wide spectrum of action, got in 1958 Produce in capsules for 0,15-0,3 grammas, and in solution for 0,25 grammas in an ampoule for B/B and B/M introductions. Day's non-permanent dose makes 0,45-0,6 grammas. Duration of course of treatment of rifampicin is 4 - 6 - 8 months. Blocks RNC-polymerase and biosynthesis RNC, what result is brakes growth of MBT. Shows the expressed hepatotoxic effect. Operates on the endo- and outcellular

MBT. Before setting necessarily conduct functional hepatic tests. For the prophylaxis of hepatotoxic action of rifampicin appoint carsil, essenciale, silibor.

Pirazinamid (tizamidum) (*Pirazinamidi*), (Z) is chemo preparation of specific action on MBT. Was synthesized in 1950 year. Produce as pills on 0,5 g. Non-permanent day's dose - 1,5 - 2,0 g. Per oral accept. Duration of course of treatment is 6 - 8 months. Z suppressions consumption of oxygen by MBT, what blocks their growth. Z operates only on endocellular MBT. Shows a hepatotoxic effect. Vitamins of group B, lipocain, methionine, hepatoprotection is preparations, reducing the toxic displays of pirazinamid.

Etambutolum (*Ehambutolum*), (*E*) is synthetic chemopreparation of the directed action only on MBT. Produce in pills for 0,4 grammas. Day's non-permanent dose is 1,2 - 1,6 grammas., per oral accept. Duration of course of treatment is 6 - 8 months. E suppressed vital functions of MBT in the period of mitosis. Causes the impression of visual nerve which shows up violation of perception colors. The vitamin of a is diminished by the toxic action of etambutol. Operates on out of and endocellular MBT.

Most sick TB ATP carry good without any special by-reactions on preparations. However for some patients the displays *of indirect action of ATP* are marked is any undesirable reaction, predefined pharmacological properties of medication, which is observed exceptionally at his use in doses, made to order for treatment, that is why the timely warning of toxic and allergic effects of medications is important part of chemotherapy.

The indirect actions of chemical preparations are divided into the followings: 1. Allergic reactions (arise up in 80-90% in the first 2 weeks of treatment);

- 2. Toxic reactions (develop in 70% patients in 2-3 months of treatment);
- 3. Toxico-alergic reactions (develop in 2-3 months and later).

By-reactions can also arise up at overdose of medications, and also when mass of body and age of patient is not taken into account.

Impermissible monotherapy TB, because assists development of resistant of MBT to preparation. All of ATP must be accepted <u>1 time per a day, approximately after</u> 30 minutes after-meal (rifampicin to the meal).

3. PATHOGENETIC THERAPY OF TB

Pathogenetic therapy is directed on the decision of such tasks:

- 1. Diminishing of the exudates-pneumonic phenomena is in the hearth of defeats, accelerations of his resolve and cicatrisation with minimum remaining changes.
- 2. Correction of the broken TB intoxication and antituberculosis preparations of exchange processes and dysfunctions of different organs and systems.
- 3. Stimulation of inflammatory processes.

Except for polichemotherapy utilize such methods of pathogenetic treatment as: hygien-dietic mode, physical therapy, sanatorium-resort.

Hygien-dietic mode:

- bed for hardness patients to 2 weeks
- sparing -3 5 hours in a bed in the day-time
- training for a convalescent, 3 hours abed in the day-time in 3-6 months of treatment.

Normalization of exchange of matters: valuable feed and desintoxication: a mandatory member of holiatry is the special food rations for sick TB. In rations take into account

the power necessities of patient taking into account the mode. In a feed foresee optimum correlation of albumens, grew fat carbon hydrates, vitamins and mineral salts taking into account the physiology necessities of patient. On 1 kg of weight of patient: albumens are 2 grammas. grew fat 1,5 grammas. and carbon hydratess are 7 grammas. The mode of reception of meal is 4-5 times per a day, by small portions. All of the transferred requirements are answered by a diet N_2 11 after Pevzner. I am needed slowly, carefully chewing a meal.

Symptomatic and nosotropic therapy of tuberculosis

Symptomatic therapy is setting a patient in the case of necessity febrifuge medications, anther cough and solvencies, analgetics. At accompanying diseases and disorders of function of other organs apply medical preparations which are directed on their normalization.

Pathogenetic therapy includes for itself: hormonotherapy, ant inflamation, desintoxication, vitaminotherapy, and immunotherapy. Application of nosotropic therapy is grounded next to antimycobacterial preparations in 3-4 times increases efficiency of treatment.

Hormonal preparations. Among them the special place is occupied by the hormones of bark of adrenal: prednisolon, which have expressed ant inflammation desensitizing an action. The antiallergic action of glucocorticoids (GK) is carried out by sharp oppression of products of histaminum which appears at cooperation of complex antigen-antibody with cages. Ant inflammation their effect is related to the antihunt operating on biological membranes, by oppression of synthesis or freeing of neurohumors of inflammation, including prostaglandin. GK is also diminished formation of collagen and that is why prevent the surplus forming of rough fibred material, cicatrisation's at its application takes a place with predominance of resolve of exudates and infiltration changes. However much oppressions of proliferation of fibroblasts and formation of granulation tissue under act of GK can have a negative value, that is why these preparations are applied only on a background valuable ABT. In connection with such features of action of GK, appoint on the initial stages treatment and at allergic by-reactions on ATP.

In treatment TB the chart of setting of prednizolon, offered professor A.G.Yareshko is utilized in 1980 Thus prednizolon in a dose 20 mg are accepted in the morning in 7-8⁰⁰, across a day, no less than 2 months. Prednizolon is got by all the patients are first diagnosed on TB in default of contra-indications.

Detoxication therapy is rotined during intoxication, in the case of progress of TV of process or threat of transition of him in a chronic form. Includes for itself transfusion of preparations of blood (plasma, albumin, protein); electrolyte solutions (solution of Ringera-lokka 200-400 ml of in vein droplet 1 time per days, reosorbilat 200 ml of e/v droplet 1 time per days); salt solutions, glucose.

Desensitizing antihistamines (suprastin, diazolinum, loratidin, and tavegil) appoint for the removal of allergic component of inflammatory process and at allergic reactions on ABP.

At TB immune processes are always violated, especially T-sells of immunity. Setting *of immunostimulation facilities* is therefore justified: timalin behave to them, T-activin, to sodium of nucleinat, splenin et al. They are appointed under control the indexes of the immune state of organism.

Preparations, directed on normalization of exchange processes and function of internals, play a large role in the holiatry of patients on TB. Exchange violations and

disfunction of internals organs can be predefined TB intoxication, accompanying diseases, and also influence of ATP.

Isoniazidum results in the deficit of vitamins of group B, etionamid and protionamid violate the exchange of nicotine acid, that is why at treatment preparations of group of GINA appoint the courses of thiaminum and pyridoxin, at treatment of etionamid and protionamid is a vitamin B of ATP is had certain hepatotoxic action, that is why on a background a chemotherapy, especially at persons with the accompanying diseases of liver, it is necessary to appoint hepatoprotection (essenciale, carsil, LIV-52, silibor, livolin).

At TB the processes of peroxidated oxidization of lipids are activated, antoxidation defense of organism goes down, hypoxia develops.

Stimulation of reparative processes and cicatrisation of cavities utilize treatment on more late stages, when a threat of forming of rough fibrosis changes is. The extract of aloe (1 ml hypodermic, daily), vitreous body (1-2 ml hypodermic, daily), Plasmol (1 ml hypodermic, daily), belong to them, depend placentas (2 ml hypodermic, 1 time per 7-10 days). All of these preparations have positive influence on heterospecific reactivity of organism, tissue exchange, and instrumental in more perfect cicatrisation, diminish forming of rough cicatricles changes.

Physical therapy methods of treatment

Utilized with the purpose of direct influence on TB process, warning of his complications and liquidation of separate symptoms. The purpose of setting of physiotherapy on the initial stage of treatment is an increase of concentration of ATP in the area of defeat (tissue electrophoresis with ATP); diminishing of bronchial obstruction, hypoxia, ant inflammation, desensitizing, immunmodulation action (informatively wave therapy, inhalations et al). On more late stages the purpose of physical methods of treatment is stimulation of processes of resolve, increases of permeability of tissue membranes for ATP, improvement of reparation processes, accelerations of cicatrisation of cavities, to prevention of surplus formation of connecting fabric.

Sanatorium-resort treatment

The basic medical factors of climatotherapy is a maximal stay on fresh air with low humidity, small fluctuations in a temperature and atmospheric pressure, sun-baths are dosed, LFK.

4. SURGICAL METHODS OF TREATMENT

Taking into account that TB of lights is an inflammatory infectious disease, surgical methods must be examined as a fragment of holiatry, but not alternative method.

The surgical methods of treatment are divided by radical, collapsosurgical and intermediate. To radical take the followings operations: pulmonectomy, lobectomy, segmentectomy, combined resection. Radicalism of operation consists in the delete of basic cell of the impression. Specific therapy proceeds after an operation.

At collapsosurgical operations form terms for atelectaz of lung and healing of cavity without its delete. Collapsosurgical operations is: pneumothorax, pneumoperitoneum, thoracoplastyc.

To the intermediate operations take operations without the mediocre operating on a cavity (cavernothomy, cavernuplastic, drainage of cavity, dressing bronchial tube). *Testimonies* to surgical treatment can be planned (absolute and relative) and exigent.

Absolute a testimony is to surgical treatment:

1) proof secreting MBT after 6 monthly ant tuberculosis therapies at presence of cavity;

2) remaining changes are enlargement, a particle (lung) is blasted, and stenos of bronchial tube are expressed;

3) suspicion on combination of TB with malignant new formations;

4) large fibrous-cavern lung TB, tuberculem without secreting MBT;

5) thin-walled cavities without secreting MBT from the epidemiology considering (workers of child's establishments).

Relative testimonies to surgical treatment take a place at widespread form of TB or violation of vitally important functions of organism.

Exigent testimonies to surgical treatment:

1) complication TB of process pulmonary bleeding which does not succeed to be stopped with conservative methods;

2) spontaneous pneumothorax.

Contra-indication to surgical treatment: heart attack of myocardium, defect of heart, heart insufficiency, hypertensive illness, disease of blood, amyloidosis of internals with violation of their function.

Case of disease	The initial phase	Phase continuation		
	(daily / or intermittent)	(Daily / or intermittent)		
New case	2 HRZE	4 HR або 4 H ₃ R ₃		
Earlier treated patients	2 HRZE	4 HR		

5. STANDARD MODES OF TREATMENT TB:

The standard regime of chemotherapy for the 4th category are: 8 Z Cm Lfx Pt(Et) Cs (± PAS)/12Z Lfx Pt(Et) Cs(± PAS)

Materials are for self-control:

A. Task for self-control (tables, charts, pictures, graphic arts):

B. Task for self-control

- 1. A patient is 40 years. In childhood had a contact with to the patients on TB. At hiring, by fluorographi in 1 segment right found out lungs area of darkening 2 S in the diameter of middle intensity with clear even contours. In adjoining pulmonary tissues the single are determined small intensity of focal shads. Complaints are not present. Objectively are without pathology. Blood test within the limits of norm. Not found out MBT. A diagnosis is set: tuberculome 1 segment of right lungs, MBT-. What treatment is it necessary to appoint a patient in an intensive phase?
- 2. To the patient 47 years a diagnosis is set: caseous pneumonia of right is lungs. The state is sick heavy. Temperature of body of 39-40°C, a cough is marked with sputum, shortness of breath at peace. A patient is HIV-infected. Above an overhead particle right lungs dullness is determined. Breathing is bronchial. Hearkened to the two-bit of different calibers moist wheezes. Blood test L-12,4X10⁹/l, to RSE 38 mm/hour. Roentgenologic: overhead particle right lungs totally black-out, on a background darkening the plural areas of clearing up are determined. In lower particles both the

lungs determined small intensity of focal shade with unclear contours. In sputum found out MBT.

What etiotropic therapy does need to be added to ATP?

3. At fluorographyc inspection of patient 27 years in the II segment right lungs found low-intensity focal shads with unclear contours. Complaints are not present. Objectively is without pathologists. Blood test within the limits of norm. The diagnosis of TB is set.

What category does the sick fall into? What etiotropic therapy is it necessary to appoint a patient in an intensive phase?

4. Patient to T. 18 years acted on an occasion FTB. Roentgenologic: rigth in the second segment single focal shads of small intensity without the clear contours of MBT (-), to RSE – 5 mm/hour, L- 7,5·10⁹/l.
To put a previous diagnosis. To work out a plan of inspection. To work out a

plan of treatment.

5. Patient of 32. Disturbs a weakness, increase of temperature to 38° C, cough with the sputum. Marked worsening of feel two weeks ago. It is not found out pathologies objectively. Blood test: L - $9,2x10^{9}/1$, lymphocytes - 22%, to RSE - 25 mm/hour. On a survey sciagram in the VI segment left lungs the area of darkening is determined 4x4 cm, to small intensity, with unclear contours and clearing up in a center. The diagnosis of infiltration TB of left is set lungs. Found bakterioskopic of MBT.

What etiotropic therapy will appoint a patient in an intensive phase?

Literature

Basis:

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- 2. Phthisiology : textbook / V.I. Petrenko, O.K. Asmolov, M.G. Boyko [et al.] ; edited by V.I. Petrenko. Kiev : AUS Medicine Publishing, 2015. 416 p.

Supplementary

1. Tuberculosis : manuel for teacher, students and doctors / A.G. Yareshko, M.V. Kulish. – Poltava : Poltava Literator, 2011. – 156 p.

Information resources

1. Childhood TB for Healthcare Workers: an Online Course. – Access mode: https://childhoodtb.theunion.org/courses/en

2. WHO: tuberculosis. – Access mode: http://www.who.int/tb/en/